page 18, lines 20-25 of the subject specification. Applicants canceled claims 14 and 15 without prejudice. Claim 1 has also been amended to be directed to "human" subjects. Support may be found in canceled claims 14 and 15. These amendments raise no issue of new matter. Thus, claims 1-13, and 16-26 will be pending upon the entry of this amendment.

Restriction Requirement Withdrawn

The Examiner stated that applicant's arguments in Paper 5, filed 3/6/00, regarding the restriction requirement issued in Paper 4, filed 1/27/00, have been taken into consideration and found to be persuasive. Therefore, the Examiner stated that the restriction requirement is withdrawn and claims 1-26 are pending in the current application.

Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claims 1-16 and 26 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described n the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that in the various exemplifications provided

in the specification, only the polypeptide of SEQ ID NO:2 is utilized. The Examiner stated that the specification does not indicate what distinguishing feature of any other fragment of CD39 must exist for utilization in the claimed invention, other than that it acts to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism in the subject or that it reduces cerebral infarct volumes, neurological deficit and mortality. Thus, the Examiner stated that the scope of the claims include numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted, yet the specification does not provide guidance as to specific changes to make. The Examiner alleged that since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, such as which specific protein domains confer the ability to inhibit platelet aggregation, and because the genus is highly variant, the ability to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism in the subject is insufficient to describe the genus.

In reply, applicants traverse the rejection and maintain that the claimed invention is fully described in the specification.

The claimed invention is directed to, *inter alia*, methods for treating or preventing stroke in a human subject which comprises administering a CD39 polypeptide (SEQ ID NO. 1) or an active fragment thereof which inhibits adenosine diphosphate-mediated

platelet aggregation by increasing adenosine diphosphate catabolism to the subject without increasing intracerebral hemorrhage in the subject. Clearly, a CD39 polypeptide (SEQ ID NO:1) is fully described in the specification. Furthermore, "an active fragment" of a CD39 polypeptide is fully described in the specification. An active fragment of CD39 polypeptide is further characterized in the pending claims as one which inhibits adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphoshate catabolism in a subject.

There is sufficient written description in the specification regarding variants of soluble CD39. For example, on page 8, lines 25-35, the specification recites:

> Variants in amino acid sequence of solCD39 are produced when one or more amino acids in naturally occurring SolCD39 is substituted with a different natural amino acid, an amino acid derivative, a synthetic amino acid, an amino acid analog or a non-native amino acid.

The specification also recites that variants of soluble CD39 includes "biologically active fragments of naturally occurring SolCD39." Examples of such biologically active variants are variants which have one or more conservative amino acid substitutions. Furthermore, the specification provides guidance as to how the variants will compare to the naturally occurring soluble CD39. Specifically, the specification recites: "such substitutions typically would have minimal influence on the secondary structure

and hydrophobic nature of the SolCD39." See page 9, lines 1-5 of the subject specification. See also the subject specification, pages 9-12, line 31. Clearly, the variants encompassed by the claimed invention could have the characteristic that substitutions of amino acids would result in a minimal change of the secondary structure or hydrophobic nature of the soluble CD39. There is an extensive description in the specification as to other types of biologically active fragments of CD39 which are encompassed by the claimed invention. In all cases, the specification describes these fragments or variants of soluble CD39 as having the ability to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism.

Applicants maintain that the claimed invention is fully described in the specification and that one of skill in the art would have understood that the applicants had possession of the claimed invention at the time of filing. In view of this discussion, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 1-26 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a transgenic mouse homozygous deletion in CD39 and use in identifying compounds which inhibit platelet aggregation via the ADP pathway; and the use of soluble CD39 in the treatment and prevention of

thrombotic and ischemic disorders in mice and BIBU52 in rhesus and marmoset monkeys (Guth et al., abstract), does not reasonably provide enablement for the use of any CD39 fragment or full-length CD39 (SEQ ID NO:1) in treating or preventing stroke; or the use of an animal model of in testing for compounds which inhibit platelet aggregation via any pathway.

The Examiner stated that as stated in the preceding section, the specification fails to disclose the identity of any CD39 fragment, other than the exemplified SEQ ID NO: 2, with the ability to inhibit platelet aggregation by increasing adenosine diphosphate catabolism or that the full length CD39 (SEQ ID NO: 1) demonstrates said ability. The Examiner stated that although the specification provides a general disclosure on the methods of generating additional CD39 variants (pg 8, line 25-pg 12, line 10), said disclosure does not provide specific details on the composition of a fragment which is necessary to inhibit platelet aggregation. Therefore, the Examiner stated that in the absence of teachings disclosing the ability of the full length CD39 or any variant other than the soluble form of CD39 (claim 5) to inhibit platelet aggregation or ADPase activity *in vivo*, or even to maintain its biological activity *in vivo* for long periods of time following i.v. administration (see Gayle et al, pg 1853, col 1, "Pharmacokinetic analysis"), the artisan would be required to practice undue experimentation to utilize any other fragment of CD39 such that any therapeutic outcome could occur.

The Examiner stated that the specification also fails to provide an enabling disclosure for a method of treatment or prevention of any stroke in any subject other than the exemplified mouse. The Examiner stated that the applicant asserts on page 25, lines 25-26, of the specification that the exemplified mice are an art accepted model for stroke injury and could therefore be used to analyze the occurrence of latent pro-thrombotic phenotype and the effect of administering CD39 to inhibit platelet aggregation in vivo (pg 34, lines 17-20). The Examiner stated that it is noted that none of the teachings incorporated by reference into the specification to support the use of the mouse ischemic model, such as reference number 2, 3, or 25, have been provided to the Examiner. The Examiner stated that as such, they have not been taken into consideration. Additionally, the Examiner stated that it was well known in the art at the time of the invention that proteins involved in thrombosis displayed different levels of activity between specifies. For example, the Examiner stated that Fay et al (Arteriosclerosis, Thrombosis, and Vascular Biology, October 1996, 16(10): 1277-1284) demonstrated that porcine plasminogen activator inhibitor-1(PAI-1) displayed a significantly higher level of activity than human PaI-1. Therefore, the Examiner stated that one of skill in the art would be required to practice undue experimentation to extrapolate the method of administering the soluble form of CD39 exemplified by the specification, to a non-mouse subject, such as human, such that a predictable level of treatment or prevention of stroke could occur.

Lastly, the Examiner stated that the specification fails to provide an enabling disclosure for the use of an animal model to test for compounds which inhibit platelet aggregation by inhibiting ADP catabolism by measuring said compounds effect on all types of platelet deposition (claim 17c). The Examiner stated that platelet aggregation during thrombosis is induced by collagen, ADP, and a thrombin receptor-activating peptide (Guth et al, abstract). The Examiner stated that in as much as soluble CD39 has been disclosed by the art to be an ADPase, the claimed invention is not enabled for testing compounds which are not previously known to be ADPase's because the artisan would not be able to discern if any platelet aggregation resulting from use of a test compound acted via collagen or thrombin receptor-activating peptide pathway or ADPase pathway. The Examiner stated that the specification does not teach the manner of blocking the collagen or thrombin receptor-activating pathways in the animal model to ensure that any effect the compound had on the inhibit of platelet aggregation was through the ADPase pathway versus via the inhibition of the collagen or thrombin receptor-activating pathways. Therefore, The Examiner stated that one of skill in the art would be required to practice additional and undue experimentation to identify the pathway be which any compound might inhibit platelet aggregation in the claimed transgenic CD39.

In reply, applicants traverse the rejection and maintain that the claimed invention is fully enabled by the subject specification.

First, applicants remind the Examiner that working examples of a particular claimed invention is not required for patentability. However, applicants point out that there are at least two working examples of soluble CD39 or biologically active variants thereof which are included in the subject specification and the Examiner has so acknowledged this. In addition, the subject specification gives a detailed discussion of what are other possible changes which could be made to the amino acid sequence of CD39 (provided in the specification on pages 7-12) which one of skill in the art would appreciate would produce a variant of the soluble CD39, but which would not affect the ability of the resulting molecule to function in (1) inhibiting adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism or (2) without increasing the incidence of intracerebral hemorrhage in a subject. Both (1) and (2) above are measurable, functional characteristics which one of ordinary skill in the art at the time would have know how to assess without undue experimentation. Indeed, applicants' specification provides extensive guidance for carrying out assays in order to analyze either of the two above-listed criteria.

Undue experimentation is not the same as some experimentation. Applicants submit that one of ordinary skill in the art at the time of filing, would have routinely carried out platelet aggregation assays and/or in vivo assays utilizing a stroke animal model to assess the ability of a candidate CD39 variant to work functionally without increasing intracerebral hemorrhage in the animal subject.

Applicants maintain that such experimentation would have been routine and not undue.

Applicants also submit that one of skill in the art would have understood that successful experimental results obtained using a soluble CD39 biological variant in a mouse model of stroke would have been reasonably predictive of the ultimate use of the variant in humans. This would have been the case because successful treatment of a mouse model of human disease has been well accepted by those of skill in the art as being reasonably predictive of success in human therapy.

Applicants have shown that when soluble CD39 was given to mice in model of stroke, there was an improvement of stroke outcome. The mice had improved blood flow, reduced thrombosis, improved neurological function, smaller cerebral infarcts as compared to mice given a negative control vehicle. Applicants attach hereto a copy of an abstract which was presented at the American Heart Association in November of 1999 (attached hereto as **Exhibit A**). The data presented in the specification show that unlike other anti-platelet therapies for stroke (such as aspirin), soluble CD39 or biological variants thereof, can improve stroke outcome without increasing intracerebral hemorrhage. In sum, the murine model system of stroke is an accepted model of stroke and one of ordinary skill in the art would have had a reasonable expectation of success of carrying out the claimed invention.

As to the references 2, 3 and 25, applicants will supply these references to the Examiner shortly as a Supplemental Information Disclosure Statement.

In addition, applicants emphasize that it would have been considered to be routine experimentation to optimize the dose of any particular chosen CD39 active variant. This type of experimentation is routinely undertaken by those of skill in the art in the drug development processes and as required steps when applying for FDA approval. However, although there may be many steps to this process, this type of experimentation is considered routine to one of ordinary skill in the art. For example, if one particular variant shows increased potency, then the dosage for that variant would decrease.

In addition, applicants also submit that the standards of the Federal Drug Administration which are required to be met by an applicant are not the standards for patentability before the U.S. Patent and Trademark Office. The M.P.E.P. (7th Ed. 2000) at §2164.05, page 2100-34, states that "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled." In addition, see *Scott v Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")

Furthermore, it is well settled law that enablement is not

precluded by the necessity for some experimentation. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The key word in this regard is "undue" not "experimentation." *Id.*, citing *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Thus

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the claimed invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Wands at 1404, citing *In re Jackson*, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982).

In conclusion, applicants' specification in combination with what was known to one of skill in the art as of their effective filing date would have enabled the skilled person to carry out the presently claimed invention without undue experimentation. Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Thus, applicants maintain that one of ordinary skill in the art would have been fully enabled to carry out the claimed invention without undue experimentation.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 17 and 20-24 under 35 U.S.C. §103(a) as being unpatentable over Guth et al (8/97) in view of Gayle et al (1998).

The Examiner stated that Guth et al disclose the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.e. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. The Examiner stated that Guth et al do not disclose the use of CD39.

The Examiner stated that Gayle et al disclose a recombinant soluble form of CD39 and demonstrate the anti-thrombotic activity *in vitro* by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active *in vivo* while circulating for prolonged periods of time. (Full article, abstract, Figure 1; 1858, col. 2, para. 4).

The Examiner stated that in light of Guth et al. and Gayle et al., it would have been obvious to one of ordinary skill in the art to utilize an animal model of thrombosis to test for the effect of a potential therapeutic compound on inhibiting ADP driven platelet aggregation. The Examiner stated that one would be motivated to utilize the soluble CD39 as the test compound in said model because Gayle et al had demonstrated that it inhibited platelet aggregation *in vitro* by catabolizing ADP and that it remained biological active

in vivo, thus displaying the potential to inhibit platelet aggregation in an animal under thrombotic conditions.

In reply, applicants traverse the rejection of claims 17 and 20-24 under 35 U.S.C. §103(a) as being unpatentable over Guth et al (8/97) in view of Gayle et al (1998).

Guth et al. disclose that a nonpeptidic molecule blocks glycoprotein (GP) IIb/IIIa (the alpha 1lb beta3 integrin) and inhibits platelet aggregation. There is no disclosure of decreasing intracerebral hemorrhage in the subjects treated with the nonpeptidic compound. Gayle et al. discloses inhibition of platelet function by soluble CD39 in a form which retains nucleotidase activity. Gayle et al. disclose that soluble CD39 is useful as an antithrombotic agent.

There is no teaching or suggestion in either reference, or in the combination of references, of a method for a method for determining whether a compound inhibits platelet aggregation and/or fibrin deposition by increasing ADP catabolism and does not increase intracerebral hemorrhage. Specifically, there is no comparison of stroke outcome in an animal administered said compound with that of an identical animal in the absence of the compound so as to identify a compound capable of treating or preventing thrombotic or ischemic disorders in a subject as presently claimed. Guth et al. merely disclose one nonpeptidic compound which apparently is a GP Iib/IIIa antagonist. There is no disclosure of a screening method

as presently claimed. Furthermore, there is no disclosure or suggestion of the specific steps set forth in the claimed screening method. In addition, Gayle et al. do not remedy the shortcomings of Guth et al. There is suggestion in Gayle et al. of applicants' screening method. Gayle et al. merely disclose the administration of soluble CD39 to normal Balb/c mice in order to perform a pharmacokinetic analysis of such an administration. There is no teaching or suggestion of a screening method, especially one which uses an animal stroke model.

Therefore, one of ordinary skill in the art at the time of the effective filing date of the subject application, would not have considered the claimed invention obvious in view of Guth et al. combined with Gayle et al. These references do not teach a screening method as claimed and specifically, do not teach or render obvious with a reasonable likelihood of success, the specific steps of applicants' screening method. Thus, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103 - Guth et al. In View of Gayle et al. And Beaudoin et al.

The Examiner rejected claims 25 and 26 under 35 U.S.C.§103(a) as being unpatentable over Guth et al. (8/97) in view of Gayle et al. (1998) as applied to claims 17 and 20-24 above, and further in view of Beaudoin et al. (US Patent 5,798,241).

The Examiner stated that the invention includes the compound identified via the claimed animal model and a pharmaceutical composition comprising said compound to treat thrombotic or ischemic disorders, such as soluble CD39.

The Examiner stated that Guth et al. disclose the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.e. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. The Examiner stated that Guth et al. do not disclose the use of CD39 or pharmaceutical compositions comprising such.

The Examiner stated that Gayle et al disclose a recombinant soluble form of CD39 and demonstrate its anti-thrombotic activity *in vitro* by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active *in vivo* while circulating for prolonged periods of time. (full article, abstract, Figure 1; pf 1858, col. 2, para. 4).

The Examiner stated that Beaudoin et al. teach the use of a composition of comprising mammalian ATP diphosphohydrolase with a pharmaceutically acceptable carrier to reduce platelet aggregation and thrombogenicity (claim 5; col 9, lines 34-37).

The Examiner took the position that in light of Guth et al., Gayle et al., and Beaudoin et al. would have been obvious to one of ordinary skill in the art to utilize a compound identified from an

animal model of thrombosis which displayed the activity of catabolizing ADP, such as an ATP-diphosphohydrolase, in a pharmaceutical composition to prevent platelet aggregation leading to thrombogenicity. The Examiner stated that one would also be motivated to use soluble CD39 in said composition because it had already been classified as an ATP-diphosphohydrolase exhibiting inhibition of platelet aggregation *in vitro*.

In reply, applicants traverse the rejection and maintain that the claimed invention is not rendered obvious by the combination of Guth et al., Gayle et al., and Beaudoin et al.

Applicants refer the Examiner to the discussion of the Guth et al. and Gayle et al. references hereinabove. Similarly, applicants submit that the combination of Guth et al., Gayle et al., and Beaudoin et al., do not render obvious a pharmaceutical composition as an agent to treat thrombotic or ischemic disorders in a subject without increasing incidence of intracerebral hemorrhage as recited in the pending claims. Beaudoin et al. merely report on the identification and isolation of ATPDase enzymes from bovine aorta and pig pancreas. There is a statement at column 9, lines 24-37 which states that "the aorta enzyme produced in the present invention can be introduced in the circulatory system of mammalians to reduce platelet aggregation and thrombogenicity." There is no suggestion in Beaudoin et al. of a composition which also does not increase the incidence of intracerebral hemorrhage in such a mammal. Thus, applicants maintain that Beaudoin et al. do not remedy the shortcomings of the Guth et al. and Gayle et al.

references.

In sum, applicants request that the Examiner reconsider and withdraw this ground of rejection. Applicants believe that the claims are in condition for allowance and look forward to a favorable action.

Supplemental Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and §1.97 (a)-(b), applicants would like to direct the Examiner's attention to the following documents:

1. Abstract of McTaggart, et al. (November 2, 1999) Cerebroprotective Role Of CD39 (Endothelial EctoADPase) in Murine Strain, Supplement *Circulation*, 100(18):Page I-328, 1720 **(Exhibit A);**

2. PCT International Search report of International Application No. PCT/US00/22060 dated November 14, 2000 **(Exhibit C);**

3. GenCore Accession No. WO4334,29 December 1996, BEAUDOIN et al., WO 96/32471 A2 (UNIV. SHERBROOKE) 17 October 1996 **(Exhibit D);**

4. Marcus, et al. (March 1997) The Endothelial Cell Ecto-ADPase Responsible For Inhibition of Platelet Function Is CD39, *The Journal of Clinical Investigation*, 99(6): 1351-1360; **(Exhibit E);**

5. Kaczmarek, et al. (December 1996) Identification and Characterization of CD39/Vascular ATP Diphosphohydorlase, *The Journal of Biological Chemistry*. 271(51):33116-33122 **(Exhibit F);**

6. Gayle, et al. (May 1998) Inhibition of Platelet Function by Recombinant Soluble Ecto-ADPase/CD39, *The Journal of Clinical Investigation* 101(9): 1851-1859 **(Exhibit G)**; and

7. Guth, et al. (1997) Antagonism Of The GPIIb/IIa Receptor With The Nonpeptidic Molecule BIBU52: Inhibition Of Platelet Aggression In Vitro And Antithrombotic Efficacy In Vivo, *Journal of Cardiovascular Pharmacology* 30(2):261-272 **(Exhibit H)**.

The above references are again listed on the substitute PTO Form 1449 attached hereto as **Exhibit B.** Copies of the documents listed are attached hereto as **Exhibits A-G.** The Information Disclosure Statement fee of $240.00 is enclosed herewith. Applicants request that the Examiner make these documents of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided.